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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,857	07/28/2006	Teruhiko Taishi	2006_0901A	9708

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EXAMINER	
BASQUILL, SEAN M	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
03/23/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/587,857	TAISHI ET AL.	
	Examiner	Art Unit	
	Sean Basquill	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Previous Rejections

1. Applicants' arguments, filed 2 December 2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Status of the Claims

2. Claims 1-10 have been amended, and Claims 11-21 cancelled by applicants' amendment. Claims 1-10 are presented for examination.

Claim Rejections - 35 USC § 112 First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds A1-10 and B1-29 listed on page 76 of the specification as originally filed, does not reasonably provide enablement for the entire genus of napthyridines as put forth in the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *PPG v. Guardian*, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to Chemical compounds having a napthyridine core, asserted as useful for the inhibition of HIV-1 integrase. The relative skill of those in the art is high, requiring the artisan have experience and knowledge concerning not only synthetic organic chemistry, but also aspects of medicinal chemistry including, but not limited to, screening assays designed to identify and quantify the binding activity of candidate molecules at target receptors, as well as understanding of the structure-activity relationship among compounds known to provide the desired binding functionality. That factor is outweighed, however, by the unpredictable nature of the art, in this particular case a lack of predictability in terms of structure-activity relationship and HIV-1 Integrase binding and inhibitory potential. As illustrative of the state of the art, the examiner cites Andrea Savarino, *A Historical Sketch of the Discovery and Development of HIV-1 Integrase Inhibitors*, 15 EXPERT OPIN. INVESTIG. DRUGS 1507 (2006) (hereinafter "Savarino").

Savarino describes the history of HIV-1 integrase development, in particular discussing the development of lead compounds in view of proposed rationales for their inhibitory activity. (Pg. 1511-19). In summarizing the understanding of HIV integrase, Savarino indicates that, in particular, two regions of target small molecule integrase inhibitor are understood to have particular importance to their activity in the inhibition of HIV-integrase: a keto-enol acid moiety (and functional and bioisosteric equivalents thereof) (Pg. 1513-14), and a hydrophobic, usually aromatic, portion. (Pg. 1513, 1517). A wide variety of compounds and conformations have been identified as HIV integrase inhibitors (Pg. 1510), without a clear-cut correlation between the

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[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not

structure of the compound and its activity as an inhibitor. Indeed, in addition to the moieties speculated to be of concern in the inhibition of HIV integrase, substituents distant to either the hydrophobic and keto enol acid moieties have been identified as conferring optimal properties to inhibitors. (Pg. 1514).

In sum, then, Savarino describes a field in which no clear structure function correlation is present, requiring the skilled artisan engage in arduous testing to simply identify compounds which are capable of binding to HIV integrase, let alone confer any particular inhibitory qualities thereto. The examiner's assertion is bolstered by reference to Fatima Zouhiri, *et al*, *Structure-Activity Relationships and Binding Mode of Styrylquinolines as Potent Inhibitors of HIV-1 Integrase and Replication of HIV-1 in Cell Culture*, 43 J MED. CHEM. 1533 (2000) (hereinafter "Zouhiri"), and Ya-Qiu Long, *et al*, *Rational Design and Synthesis of Novel Dimeric Diketoacid-Containing Inhibitors of HIV-1 Integrase: Implication for Binding to Two Metal Ions on the Active Site of Integrase*, 47 J MED. CHEM. 2561 (2004) (hereinafter "Long"). Both Zouhiri and Long discuss the HIV-1 Integrase inhibitory activity of compounds derived from moieties which are known to have HIV-1 Integrase inhibitory activity. In particular, both Zouhiri and Long provide data which shows that minor alterations to the structure of the compounds derived from known inhibitors can have a drastic effect on the IC50 of HIV-1 Integrase. *See Zouhiri*, Pg. 1535 (indicating minor changes in quinoline substituents can have a drastic effect on the IC50 of HIV-1 Integrase), and *Long* Pg. 2565-66 (indicating minor alterations to the dimer linker can have drastic effect on HIV-1 Integrase IC50). HIV-1 Integrase inhibitors, therefore, while potentially potent therapeutics for the treatment of HIV-related disorders, are well known to react

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"experimentation".

unpredictably to what would ordinarily seem an otherwise minor structural alteration. HIV-1 Integrase inhibitory activity, therefore, cannot be presumed without actual data from a screening assay, or some structure-activity relationship both asserted by applicants and supported by sufficient evidence to permit the skilled artisan to accept the asserted structure-activity relationship.

2. The breadth of the claims

The claims as presented encompass a substantial genus of napthyridine integrase inhibitors, where an expansive variety of substituents, both on the amide nitrogen as well as the napthyridine core, are included among the broad genera recited. As such, the claims encompass an incredible number of compounds, even when the proviso that compounds described by the formula 1-A are excluded from the scope of the claimed invention, as directed by independent Claim 1.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for practicing the claimed invention in its "full scope" as currently claimed. No reasonably specific guidance is provided concerning the utility of the compounds claimed, other than the in vitro inhibition data provided for compounds A1-10 described on pages 28-41 and 76, and compounds B1-29 described on pages 51-67 and 79 of the specification as originally filed. The utility of these latter compounds is corroborated by the data provided in the specification as originally filed.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental

evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used as HIV-1 integrase inhibitors as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no reasonable expectation of success.

Conclusion

No Claims are allowable as currently presented, however, applicants are strongly encouraged to contact the examiner to schedule an interview at which time appropriate amendments to the scope of the claims to properly claim allowable subject matter will be discussed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean Basquill whose telephone number is (571) 270-5862. The examiner can normally be reached on Monday through Thursday, between 8AM and 6PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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